DRUG EFFECTIVENESS REVIEW PROJECT

P&T Committee Brief

Drug Class Review on Cyclo-oxygenase (COX)-2 Inhibitors and Non-steroidal Anti-inflammatory Drugs (NSAIDs) Update 3

Alison Little, MD

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Center for Evidence-based Policy
Oregon Health & Science University
2611 SW 3rd Ave, MQ 280 Portland OR 97201-4950 503.494.2182 Fax 503.494.3807
www.ohsu.edu/policy/drugeffectiveness

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P & T COMMITTEE BRIEF
Non-steroidal Anti-inflammatory Drugs: Comparative Drug Class Review

Background:
Non-steroidal anti-inflammatory drugs (commonly called NSAIDs) reduce pain significantly in patients with arthritis, low back pain, and soft tissue pain. However, NSAIDs have important adverse effects, including gastrointestinal (GI) bleeding, peptic ulcer disease, hypertension, edema, and renal dysfunction. More recently, some NSAIDs have also been associated with an increased risk of myocardial infarction (MI). In the US, complications from NSAIDs are estimated to cause about six deaths per 100,000 population, a higher death rate than that for cervical cancer or malignant melanoma.

NSAIDs reduce pain and inflammation by blocking cyclo-oxygenase (COX), enzymes that are needed to produce prostaglandins. Most NSAIDs block two different cyclo-oxygenases, called COX-1 and COX-2. COX-2, found in joint and muscle, contributes to pain and inflammation. NSAIDs cause bleeding because they also block the COX-1 enzyme, which protects the lining of the stomach from acid. NSAIDs differ in their selectivity for blocking COX-2. An NSAID that blocks COX-2 but not COX-1 might reduce pain and inflammation in joints but leave the stomach lining alone. In theory, such selectivity would be expected to reduce NSAID-induced GI complications.

Purpose:
The purpose of this review is to summarize the comparative data on the efficacy, tolerability, and safety of NSAIDs when used for the treatment of chronic pain resulting from osteoarthritis (OA), rheumatoid arthritis (RA), soft tissue pain or back pain, including ankylosing spondylitis. The main efficacy measures are pain, functional status, and discontinuations due to lack of efficacy. Measurement tools are variable, and include the Visual analogue scale (VAS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Patient Global Assessment of Disease Status (PGA) and Investigator Global Assessment of Disease Status (IGA), and the American College of Rheumatology (ACR) criteria.

Tolerability and safety was evaluated by discontinuation due to any adverse event, any serious adverse event, the overall rate of adverse events, the rate of GI adverse events, the combined rate of adverse events related to renal and cardiovascular function, and the frequency of, and discontinuations due to, abnormal laboratory tests. The frequency of asymptomatic endoscopic ulcers was excluded, as they may not be clinically significant. The following NSAID currently available in the US or Canada are included in this review:

<u>Selective</u>
- celecoxib (Celebrex)

<u>Partially Selective</u>
- etodolac (Lodine, Ultradol*)
- meloxicam (Mobic, Mobicox*)
- nabumetone (Relafen)

<u>Nonselective</u>
- diclofenac sodium (Voltaren)
- diclofenac potassium (Cataflam, Voltaren Rapide*)
- diflusinal (Dolobid)
- fenoprofen (Nalfon **)
- flurbiprofen (Ansaid)
- ibuprofen (Motrin, Advil)
- indomethacin (Indocin)

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- ketoprofen (Rhodis*)
- ketoprofen XR (Oruvail)
- ketorolac (Toradol)
- meclofenamate**
- mefenamic acid
- naproxen (Naprosyn*)
- naproxen delayed release (Naprosyn SR*)
- naproxen sodium (Anaprox, Naprelan)
- oxaprozin (Daypro)
- piroxicam (Feldene)
- salsalate (Disalcid)**
- sulindac (Clinoril)
- tiaprofenic acid (Surgam)
- tiaprofenic acid sustained release (Surgam SR*)
- tenoxicam (Mobiflex)
- tolmetin (Tolectin)*

* Available in Canada
** Available in the US only

Methodology:
The Drug Effectiveness Review Project reviews all pertinent studies, solicits and accepts public input and updates reviews frequently. The original NSAID review has been updated three times. Literature searches identified 749 citations. Study eligibility is determined by pre-set criteria. Studies which did not meet these criteria with respect to study design or duration, patient population, interventions, or outcomes were excluded. Additionally, studies published in ineligible publications or not in English were excluded. The quality of all included studies was appraised.

Evidence Available:
Relevant information for this topic consists of 70 studies, including 49 randomized controlled trials (RCT), 5 meta-analyses and 2 observational studies. Another 14 studies were included for background information. The main findings summarized in this report are based largely on the Comparative Effectiveness Review (CER) of the Benefits and Safety of Analgesics for Osteoarthritis conducted by the Oregon Evidence-based Practice Center (EPC) for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program.

Key Questions and Findings:

Question #1: Are there differences in effectiveness between NSAIDs?

Effectiveness
There were no effectiveness trials that were conducted in an office-based setting or used broad enrollment criteria.

Efficacy

Celecoxib vs NSAID
The AHRQ Effective Health Care Program CER found no clear differences in efficacy between celecoxib and nonselective NSAIDs. Both were associated with similar pain reduction effects (WOMAC, VAS, PGA) in published trials of patients with OA, soft tissue pain, ankylosing spondylitis, or RA.

NSAID vs NSAID
Partially selective NSAIDs were associated with similar pain reduction effects relative to non-selective NSAIDs in short-term RCTs.

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Meloxicam - In double blinded trials of meloxicam versus other NSAIDs there were generally no differences in efficacy. However, patients taking nonselective NSAIDs were less likely to withdraw due to lack of efficacy than patients taking meloxicam in two of the trials.
Nabumetone - A fair-quality systematic review of three short-term RCTs of nabumetone for soft-tissue pain found no difference in efficacy when compared to ibuprofen or naproxen. However, based on physician assessment, the same systematic review also found placebo to be as efficacious as nabumetone in reducing pain at 7 days.
Etodolac – Etodolac and nonselective NSAIDs were generally associated with similar rates of withdrawals due to lack of efficacy, or improvements in pain, in short-term RCTs of patients with OA of the knee and/or hip.

Several recent good-quality systematic reviews by the Cochrane Collaboration found no clear differences among nonselective NSAIDs in efficacy for treating knee, back, or hip pain. Limited evidence from two trials found no difference in efficacy when salsalate 3g/day was compared to indomethacin 75 mg/day or diclofenac 75 mg/day. Tenoxicam, diclofenac and indomethacin were associated with similar effects on pain in a good-quality systematic review of 18 RCTs. An older (1985) review of tiaprofenic acid found no difference in efficacy when compared to acetylsalicylic acid (ASA), diclofenac, ibuprofen, indomethacin, naproxen, piroxicam or sulindac. A more recent RCT confirmed the similar short-term comparative efficacy of tiaprofenic acid and indomethacin.

Questions #2 and #3: Are there clinically important differences in short-term safety or adverse effects between celecoxib, other NSAIDs, or the combination of a nonselective NSAID plus antiulcer medication? Are there clinically important differences in long-term safety or adverse effects between celecoxib, other NSAIDs, or the combination of a nonselective NSAID plus antiulcer medication?

Results from the AHRQ Effective Health Care CER suggest that no selective, partially selective, or nonselective (with or without antiulcer medication) NSAID was clearly and consistently safer or associated with fewer adverse events overall than any other. Adverse events evaluated included serious GI events, cardiovascular risk, mortality, hypertension, congestive heart failure (CHF), edema, renal function, hepatotoxicity, and general tolerability. The majority of NSAID-related adverse effects have not appeared to be dependent upon long (i.e., >6 months) duration of exposure. The exception is cardiovascular risk, which has primarily been observed in trials with exposure periods that exceeded eight months in duration. However, this observation may be due in part to a small number of events in the shorter-term trials and decreased power to detect increased cardiovascular risk.

Celecoxib
With regard to GI adverse events, celecoxib seemed to offer a short-term advantage over nonselective NSAIDs, but this has not been conclusively demonstrated in longer-term (>6 months) studies. CLASS remains the longest-term trial to-date of patients with OA or RA. Results from an interim, 6-month analysis from the CLASS trial and from meta-analyses of short-term trials consistently suggest that celecoxib is associated with fewer serious GI complications than nonselective NSAIDs. However, regarding longer-term GI safety, celecoxib, diclofenac and ibuprofen were associated with similar rates of complicated or symptomatic ulcers after 12 months in the CLASS trials. MI rates and rates of thromboembolic cardiovascular events were significantly higher (approximately double) with celecoxib use compared to placebo based on results from the two most recent meta-analyses.

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Partially selective NSAID
Among the partially selective NSAIDs, meloxicam, nabumetone, or etodolac, none were associated with any clear safety advantages relative to nonselective NSAID.
Meloxicam - Results of short-term RCT generally do not suggest that meloxicam is associated with lower rates of ulcer complications than any other nonselective NSAID. It is not well-studied with regard to risk of other serious adverse events.
Nabumetone - One fair quality meta-analysis of 6 short-term RCTs found statistically significant fewer "PUB", meaning perforation, symptomatic ulcer, or bleeding, in patients taking nabumetone compared to nonselective NSAIDs, although the methods used to ascertain the endpoint are unknown. There was also a significant reduction in treatment-related hospitalizations in the nabumetone group.
Etodolac - The only evidence related to the risks of serious adverse events associated with etodolac comes from two observational studies of unknown durations. These suggest that etodolac was associated with similar PUB rates relative to non-use or naproxen.

Nonselective NSAIDs (with and without antiulcer medications)
There is strong evidence from numerous RCTs and observational studies that all nonselective NSAIDs are associated with relatively similar risks of serious GI events relative to non-use. Further study is needed to determine the potential comparative safety benefits of concomitant use of various gastroprotective agents in preventing clinical GI events. Currently, misoprostol is the only gastroprotective agent proven to decrease risk of clinical GI events, but this was at the expense of significant increases in nausea, diarrhea and abdominal pain. Otherwise, short-term RCTs show that misoprostol, double-dose histamine type-2 blockers, and proton pump inhibitors are all associated with significant reductions in risks of endoscopic gastric and duodenal ulcers when added to nonselective NSAIDs, compared to using a nonselective NSAID alone.

Results from a fair-quality systematic review of 138 primarily short-term RCTs suggest that nonselective NSAIDs other than naproxen are associated with similar risks of cardiovascular events compared to COX-2 selective NSAIDs. However, there is little evidence on cardiovascular risks from nonselective NSAIDs other than high-dose ibuprofen, diclofenac, and naproxen. High-dose naproxen was associated with a lower risk of MI compared to COX-2 selective NSAIDs. In indirect analyses, naproxen was risk neutral for cardiovascular events relative to placebo, but other nonselective NSAIDs were associated with higher risks. A recent, good-quality meta-analysis of observational studies found diclofenac associated with the highest risk, followed by indomethacin and meloxicam. Celecoxib, naproxen, piroxicam, and ibuprofen were not associated with increased risks. However, assessments of increased risk were modest (RR <2.0). Based on the results of several older observational studies, salsalate has often been considered to be less toxic than other NSAIDs. Due to the methodology employed in these studies, the reliability and clinical relevance of results is uncertain. A more recent observational study of serious GI event rates associated with salsalate found that the number hospitalizations after 14 months was similar to that of other NSAIDs. Evidence regarding the comparative safety of nonselective NSAID regarding all-cause mortality, blood pressure, CHF, edema, renal function, and hepatotoxicity outcomes is limited, and no strong conclusions could be reached regarding differential safety.

Question #4. Are there subgroups of patients based on demographics, other medications (e.g., ASA), or co-morbidities for which one medication is more effective or associated with fewer adverse effects?
There was only limited and inconclusive evidence of the comparative effects of NSAIDs

in subgroups based on demographics, other medications, or comorbidities.

Demographic subgroups

Celecoxib and naproxen had similar effects on pain and quality of life in elderly patients based on results from an original data meta-analysis of three RCTs. Celecoxib's effects on pain were also comparable to those of diclofenac when used concomitantly with Angiotensin Converting Enzyme inhibitors in a small study of all black or Hispanic patients.

Concomitant anticoagulant or aspirin use

Evidence regarding the comparative safety of nonselective NSAIDs relative to celecoxib or partially selective NSAIDs when used concomitantly with anticoagulants is inconclusive due to flaws in design. The only evidence of the comparative safety of NSAIDs when used in combination with ASA indicated that both celecoxib and nonselective NSAIDs were associated with significant increases in endoscopic ulcer rates.

Co-morbidities

Two short-term trials that compared celecoxib to diclofenac plus omeprazole or naproxen plus lansoprazole in very high-risk patients with recent GI bleeding found no statistically significant differences in recurrent ulcer bleeding or withdrawal rates due to adverse events. The only difference between the interventions was that one study did find an increase in rates of dyspepsia with celecoxib when compared to naproxen plus lansoprazole. No trials were identified that evaluated the effects of celecoxib or NSAIDs on cardiovascular and cardio-renal events specifically in high-risk patients. One observational study found that patients who were prescribed celecoxib had lower rates of death and recurrent CHF when compared to patients who were prescribed nonselective
NSAIDs.

Conclusions:

The AHRQ Effective Health Care Program CER found no clear differences in efficacy between celecoxib and nonselective NSAIDs. Partially selective NSAIDs were associated with similar pain reduction effects relative to nonselective NSAIDs in short-term RCTs. Several recent good-quality systematic reviews by the Cochrane Collaboration found no clear differences among nonselective NSAIDs in efficacy for treating knee, back, or hip pain. Results from the AHRQ Effective Health Care CER suggest that no selective, partially selective, or nonselective (with or without antiulcer medication) NSAID was clearly and consistently safer or associated with fewer adverse events overall (GI plus cardiovascular) than any other. There was only limited and inconclusive evidence of the comparative effects of NSAID in subgroups based on demographics, other medications, or comorbidities.

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